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(54) Title: WEIGHT CONTROL PRODUCT COMPRISING A SYNERGISTIC MIXTURE OF GUGGUL EXTRACT, PHOSPHATE SALT AND METABOLIC STIMULANT

(57) Abstract: This invention relates to a weight control composition, preferably in the form of a capsule or tablet, comprising a mixture of guggul extract, at least one phosphate salt selected from calcium phosphate, potassium phosphate and sodium phosphate and at least one metabolic stimulant. The composition evidences synergistic activity in reducing body weight and percent body fat in mammals. The guggul extract/phosphate salt/metabolic stimulant product also reduces plasma lipid levels and cholesterol in overweight hyperlipidemic humans. The inventive composition may also contain at least one additional component selected from phosphatidylcholine, hydroxycitric acid and L-tyrosine.

WEIGHT CONTROL PRODUCT COMPRISING A SYNERGISTIC MIXTURE OF GUGGUL EXTRACT, PHOSPHATE SALT AND METABOLIC STIMULANT

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Related Applications

This application is a continuation-in-part of U.S. Application Serial No. 09/282,296 filed March 31, 1999 Entitled WEIGHT CONTROL PRODUCT AND METHOD OF TREATING HYPERLIPIDEMIA AND INCREASING VIGOR WITH SAID PRODUCT, now U.S. Patent No. _____; which is a divisional application of U.S. Serial No. 09/179,328, filed October 27, 1998 Entitled: WEIGHT CONTROL PRODUCT AND METHOD OF TREATING HYPERLIPIDEMIA AND INCREASING VIGOR WITH SAID PRODUCT, now U.S. Patent No. _____.

Field of the Invention

This invention relates generally to a weight control product that is administered enterally to mammals in need of losing weight and/or reducing their blood plasma lipid levels. The weight control product comprises a mixture of guggul extract, at least one phosphate salt and at least one metabolic stimulant selected from ephedrine, synephrine, caffeine and mixtures thereof. The inventive product is also useful in enhancing mood states, increasing vigor and reducing blood serum lipid levels.

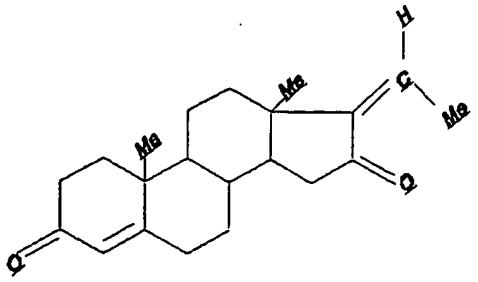
Background of the Invention

The weight control product of the present invention is designed to promote weight loss as a component of a weight control program for individuals who are overweight and desire to lose body fat and/or reduce their plasma lipid levels. The product according to the invention is consumed as a nutritional supplement and is preferably incorporated into a multi-disciplinary nutritional program, such as the American Heart Association Step One Diet.

Numerous weight control products are known in the literature. One example of a weight control product is taught in U.S. Patent 4,959,227 to Amer wherein the product has a reduced lactose content and contains dietary fiber. In similar fashion, U.S. Patent 5,104,676 to Mahmoud et al. discloses a weight loss product that utilizes a particular blend of soluble, insoluble, fermentable and non-fermentable fibers. Commercially available weight control products include Ultra-Slim Fast® which is distributed by Slim Fast Foods, a division of Thompson Medical Company, Inc., New York, New York and OptiTrim® which is available from the Clinical Products Division of Sandoz Nutrition Corp., Minneapolis, Minnesota. In addition, literally hundreds of chemical entities have been suggested as weight loss products, however, none of the prior art suggests or discloses the combined use of a guggul extract with at least one phosphate salt and at least one metabolic stimulant to result in a composition that is highly effective in reducing the weight of a mammal. This reduction in weight is accomplished, primarily, through a loss of body fat without a substantial reduction in lean body mass. The compositions according to the invention also reduce the blood plasma lipid levels of the individual. The inventive compositions have also been found

useful in enhancing mood states and increasing vigor.

A compound known as Z-guggulsterone has been identified as having the following structural formula:



The E-stereoisomer has also been identified and these ketones are known as hypolipidemic and antiplatelet aggregation agents. A process for the preparation of pharmacologically active synthetic Z and E stereoisomeric mixtures of guggulsterones is disclosed in EP0447,706 to Hamied. These compounds have also been isolated from the exudate of a plant known as *Commiphora mukul* (Hook, ex stocks) Engl. (syn. *Balsamodendron mukul* Hook) which is a small tree of the Burseraceae family, endemic in the Indian peninsula. If the trunk is etched, the plant emits a yellowish gummy exudate, which coagulates rapidly in the form of stalactites having a balsamic smell. In the ancient Sanskrit, this gum resin is called guggulu and is a product, which is still used, in Indian popular medicine for the treatment of obesity and some arthritic diseases. Recently, a lipophilic extract

has been prepared from this resin, this extract contains many classes of compounds, among which lignins, terpenes and some keto-steroids, named Guggulsterones. Hypolipidemic and platelet aggregation inhibiting activities are described for this lipophilic extract, which is normally obtained by simple resin extraction with ethyl acetate, or for Guggulsterone-Z and Guggulsterone-E, whose components in the extract are normally titrated.

By studying this resin, it has unexpectedly been found that the lipophilic extract with ethyl acetate or some fractions obtained from it when combined with a mixture of phosphate salts and metabolic stimulants, such as ephedrine, caffeine and synephrine, demonstrates outstanding weight loss, fat loss, mood elevating and hyperlipidemic properties. Further, the synergistic mixture of the present invention has demonstrated efficacy in elevating the vigor of individuals consuming it.

The guggul extract is prepared by etching *Commiphora mukul* bark and obtaining the resin. The resin is then dried, ground and subjected to extensive extraction with ethyl acetate. The collected extracts may then be treated with charcoal. After charcoal separation, the colorless solution is concentrated to obtain a thick paste, which is recovered with ethanol, and, after filtrating the insoluble matter, concentrated with complete solvent removal.

Indian Complete Specification No. 166998 discloses a method for the manufacture of a pharmaceutical composition of gugulipid in solid dosage form. The gugulipid is disclosed as being mixed with excipients and granulating agents and thereafter pressed into the solid dosage form. This reference also states that in biological tests in rats and mice with the dosage form, pharmacological

activities such as hypolipidemic, anti-obesity and hypocholesterolemic were observed.

U.S. Patent 5,273,747 to Bombardellie et al. discloses that the *Commiphora mukul* lipophilic extracts have therapeutic applications in the treatment of inflammations of the skin and external mucosa and in the symptomatic treatment of benign prosthetic hypertrophy and in the treatment of acne.

A study of the effects of guggulsterone on hypolipidemia is reported in an article by Beg, et al. in *Indian-J-Physiol-Pharmacol.* 1996 Jul; 40 (3): 237-40. This article reports that the administration of guggulsterone in daily divided doses of 75 mg for a period of eight (8) weeks together with supportive measures like a high protein diet, diuretics and hematinics resulted in a significant reduction of total serum lipid and total serum cholesterol. No mention is made of weight loss in this publication, nor is it suggested to combine the guggulsterone with a mixture of phosphate salts and metabolic stimulants to produce synergistic effects.

In an article published by Tripathia, et al. entitled "Thyroid Stimulatory Action of Z-Guggulsterone: Mechanism of Action." *Planta-Med.*, 1988 Aug; 54(4): 271-7, the authors disclose that guggulsterone is effective in stimulating the activity of the thyroid gland in rats. The guggulsterone used in this study is disclosed as being a ketosteroid isolated from the oleoresin of the dry exudate of *Commiphora mukul*. The compound was shown to counteract the thyroid suppressant activity of a known thyroid inhibitor (carbimazole).

Agarwal, et al. investigated the use of gugulipids as a hyperlipidemic agent in *Indian-J-Med-Res.* 1986 Dec; 84:626-34. In similar fashion, guggulsterones

have also been found to be very effective in reducing total cholesterol levels and LDL levels. Nityanand et al. report in "Clinical Trials With Gugulipid, A New Hyperlipidaemic Agent" *J-Assoc-Physicians-India*, 1989 May; 37(5): 323-8, a multi-center clinical trial with 205 patients over a twelve (12) week period. A gugulipid dose of 500 mg twice daily after eight (8) weeks showed a significant lowering in the serum cholesterol (average 23.6%) and serum triglycerides (average 22.6%). The study also used colfibrate as a comparative. The average fall in serum cholesterol and triglycerides for the gugulipid was 11% and 16.8%, respectively, and with colfibrate, 10% and 21.6%, respectively. The lipid lowering effect of both compounds became evident three (3) to four (4) weeks after beginning enteral consumption. Nityanand et al. also reported that hypocholesterolemic patients responded better to gugulipid therapy than hypertriglyceridemic patients who responded better to colfibrate therapy. HDL-cholesterol was increased in sixty percent (60%) of the cases who responded to the gugulipid therapy. In contrast, colfibrate had no effect on HDL-cholesterol.

U.S. Patent 5,690,948 to McCook et al. discloses gugulipid (a lipophilic ethyl acetate extract from *C. Mukul or C. Wightii*) and an alcoholic fraction of gugulipid as an antisebum and/or antioxidant for skin care compositions. This patent does not suggest nor disclose the combination of gugulipid with a mixture of phosphate salts and metabolic stimulants to create a synergistic weight control product. One important aspect of the inventive weight control product is the synergistic effect that is obtained by combining the guggul extract with a sufficient amount of phosphate salts and metabolic stimulants.

A number of studies have recently investigated the affect of calcium

phosphate, potassium phosphate and sodium phosphate to increase the basal metabolic rate (BMR) and increase thyroid activity. For example, see Nazar et al. "Phosphate Supplementation Prevents A Decrease In Triiodothyronine And Increases Resting Metabolic Rate During Low Energy Diet" *J-Physiol-Pharmacol.* 1996 Jun; 47(2): 373-83. In the Nazer et al. study thirty (30) overweight women participated in an eight (8) week slimming program consisting of a self controlled, low energy diet (4.2 mj per day) supplemented with highly viscous fibers and mineral tablets containing calcium, potassium and sodium phosphates. This was a double blind, cross-over study. During periods of phosphate supplementation, the resting metabolic rate (RMR) increased by approximately twelve percent (12%) ($p < 0.05$) in Group One and nineteen percent (19%) ($p < 0.05$) in Group Two. The study reported that there were no differences between groups in the plasma insulin, catecholamine, growth hormone, cortisol and testosterone levels. It was also reported that phosphate supplementation did not effect plasma lipids or blood glucose concentration.

Kaciuba et al. reported in "Effective Phosphate Supplementation On Metabolic and Neuroendocrine Responses To Exercise And Oral Glucose Load In Obese Women During Weight Reduction", *J- Physiol-Pharmacol* 1993 Dec; 44(4): 425-40, a study wherein 36 obese women participated in a four (4) week weight reducing program. All of them complied with a low fat diet of approximately one thousand (1000) calories per day with high viscous fiber capsules as a basic supplement. Group One (n=18) received mineral tablets containing mainly calcium and potassium phosphates while the remaining subjects (Group Two) were given a placebo tablet. This study reports that weight loss

during energy restriction was not affected by phosphate supplementation, however, the consumption of the phosphates caused a significant increase ($p < 0.05$) in the resting metabolic rate.

For every form of life, phosphates play an essential role in all energy transfer processes such as metabolism, photosynthesis, nerve function, and muscle action. The nucleic acids, which among other things make up the hereditary material (the chromosomes) are phosphates, as are a number of coenzymes. The phosphates are based on phosphorus atoms tetrahedrally surrounded by oxygen atoms, with the lowest member of the series being the simple PO_4^{-3} anion (the orthophosphate ion). A phosphorus compound of major biological importance is adenosinetriphosphate (ATP), which is an ester of sodium tripolyphosphate, a compound widely employed in detergents and water softening compounds. Practically every reaction in metabolism and photosynthesis involves hydrolysis of this tripolyphosphate to its pyrophosphate derivative, called adenosinediphosphate (ADP).

Phosphates are used as dietary supplements for patients who are unable to get enough phosphorus in their regular diet, usually because of certain illnesses or diseases. Injectable phosphates are administered only by or under the supervision of a health care professional. Various forms of phosphates are available without a prescription. Often tablets and powders are dissolved in a liquid prior to consumption. This is done to avoid or lessen possible side effects which include diarrhea, nausea, vomiting and stomach pain.

Metabolic stimulants, as used herein and in the claims, means those compounds that increase the rate of fuel consumption in an animal, excluding the

phosphate salts. For example, as discussed above, phosphate salts have been reported to increase the resting metabolic rate in humans. Other metabolic stimulants, such as amphetamines, cocaine, ephedrine, synephrine and caffeine are also know. Many of these compounds were originally isolated from plants and can now be synthesized chemically to produce discrete molecular entities.

Plants having pharmacological and biological activity have been the basis of treatment of humans from time immemorial. Every country in the world has lists of herbal remedies for the treatment of diseases and various human conditions. The foundations of the modern drug industry are essentially based on the discovery of active compounds from plants, for example, the isolation of morphine from the opium poppy by Frederic Serterner, quinine from the cinchona tree, cocaine from the leaves of coca shrubs and a host of other drugs such as atropine, curate, reserpine and the like. The use of pharmacologically or biologically active plant extracts is well known and it is also known that the active compounds can be isolated and purified from the plant extracts to obtain the therapeutic compositions.

Ephedrine is an alkaloid that has been used as a decongestant and is obtainable from plants of the genus *Ephedra*, particularly the Chinese species *E. sinica*. It has been used in China for more than 5,000 years to treat asthma and hay fever. Ephedrine/pseudo-ephedrine is the active components, derived from the natural herb Ma Huang. Ephedrine and pseudo-ephedrine are stimulants much like coffee and tea. Ephedrine stimulates the adrenal glands which increases the metabolic rate. Ma Huang has also demonstrated the promotion of thermogenesis (the burning of fat). The pseudo-ephedrine used in many over-the-counter (OTC) drugs is typically synthetic and is used in products such as Tylenol Allergy/Sinus;

Sudafed; and NyQuil. These products are considered safe by the U.S. Food and Drug Administration (FDA) and have recommended dosages of up to 60 mg of pseudo-ephedrine up to four (4) times per day (240 mg total per day).

Sida cordifolia has been used for over two thousand years to treat bronchial asthma, colds and the flu, chills, headache, nasal congestion, wheezing and coughing and edema. The stem of this plant contains a number of active compounds including small amounts of an essential oil, and most important, 1 to 2% by weight alkaloids composed mainly of ephedrine and pseudo-ephedrine, with ephedrine ranging from 20 to 90% by weight, depending on the source of the plant. Sida cordifolia is an herbal medicine which is an extract of the *Sida cordifolia* plant. The importance of Sida cordifolia becomes apparent as it contains ephedrine alkaloids, common to the *Ephedra* plant (also known by its Chinese name, Ma Huang). Sida cordifolia contains lesser quantities of the alkaloids than Ma Huang and is therefore regarded as a weaker stimulant on the cardiovascular and central nervous systems. Furthermore, Sida cordifolia contains other bronchodilating principles which Ma Huang does not have, in particular, vasicinone, vasicine, and vasicinol.

Caffeine has been consumed by millions over the history of mankind and can be obtained from coffee beans, tea, kola nut, guarave (*Paullinia capana H.B.K.*), maté and cacao. Caffeine is a nitrogenous organic compound of the alkaloid group; substances that have marked physiological effects. Pure caffeine (trimethylxanthine) occurs as a white powder which has a melting point of 238°C. Caffeine is present in ground coffee in amounts ranging from between 0.75 and

1.5% by weight. The average cup of coffee thus contains about 100 mgs of caffeine. The caffeine content of tea varies greatly depending on the strength of the tea, but averages about 40 mg per cup. Green tea is an especially good source of caffeine.

Guarana is a creeping shrub native to the Amazon. Guarana is also known as Brazilian cocoa and is of the family *Sapindaceae*, the genus *Paullinia* and the species cupana. Guarana is a stimulant that has several times the caffeine level of coffee. It is commonly promoted in the health food industry, among other uses, as a weight loss and smoke cessation aid. In the United states, Guarana is generally regarded as safe, with a caffeine content of 3 to 5% by dry weight. In comparison, coffee beans have approximately 1 to 2% caffeine by dry weight, and dry tea leaves vary from 1 to 4% by weight.

Extracts from the bitter orange plant have been used for centuries in China for the treatment of ailments such as phlegm and indigestion. Extracts from the bitter orange plant have been analyzed and found to contain synephrine, a natural alternative to ephedrine. Synephrine is similar to ephedrine, pharmacologically, without the intense stimulatory side effects. Bitter orange extract has been combined with *Garcinia Cambogia* and marketed as a weight management product. Bitter orange (*Citrus Aurantium*) has also been combined with St. John's Wort and has been marketed as an appetite suppressant and mild stimulant to the adrenal glands for thermogenesis.

Neroli Oil (a.k.a., Neroli Bigarade oil (*Citrus bigaradia*), Bigarade oil, bitter orangeflower oil, orangeflower bitter oil (*Citrus aurantium L. var amara*)

and citrus bigaradia oil are the essential oils distilled from the flowers of the cultivated bitter orange tree, Citrus Aurantium, (subspecies *amara*). Zhi Shi is the oriental name for an extract that is water decocted (concentrate) from the immature fruit of the bitter orange plant. Suggested dosages are 1 to 2 grams 2 to 3 times per day.

U.S. Patent No. 5,055,460 to Friedlander relates to a method for producing or maintaining weight loss by administering to a human a composition containing an effective amount of caffeine, aspirin and ephedrine. Numerous pharmaceutical compositions, like that disclosed in the '460 patent, have been developed with the purpose of stimulating thermogenesis in animals to induce a weight loss.

Numerous studies have reported that mixtures of ephedrine and methylxanthines, such as caffeine and theophylline have been reported in humans. These studies suggest that ephedrine/methylxanthine mixtures are more effective than ephedrine given alone. However, reports have also been published suggesting that caffeine has no potentiating effect on the action of ephedrine. However, a need continues to exist for improved weight loss compositions which are safe, effective and exhibit reduced side effects in humans.

While the prior art discloses the use of guggulsterones to reduce blood plasma lipid content, the use of phosphates to decrease triiodothyronine and increase resting metabolic rate, and the use of stimulants such as ephedrine, caffeine and synephrine, there is no suggestion or disclosure of combining these materials to achieve a synergistic effect in weight control and the surprising benefits of enhanced mood states and increased vigor.

Summary of the Invention

There is disclosed a weight control product comprising guggul extract, at least one phosphate salt and at least one metabolic stimulant selected from ephedrine, caffeine, synephrine and mixtures thereof. In a preferred embodiment, the metabolic stimulants are obtained from herbal sources such as Ma Huang, *Sida cordifolia*, coffee beans, green tea, guarave, cacao, bitter orange and mixtures thereof. There is also disclosed a method for reducing the plasma lipid levels and/or cholesterol levels in a mammal, said method comprising the step of administering to said mammal a therapeutically effective amount of a composition comprising guggul extract, at least one phosphate salt and at least one metabolic stimulant selected from ephedrine, caffeine, synephrine and mixtures thereof. There are also disclosed methods for enhancing the mood states and vigor of a mammal, the methods comprising the enteral administration of the inventive guggul extract/phosphate salt/metabolic stimulant composition.

There is further disclosed a guggul extract/phosphate salt/metabolic stimulant weight control product comprising at least one additional component selected from the group consisting of phosphatidylcholine, hydroxycitric acid (HCA) and L-tyrosine. In yet another embodiment of the invention, the weight control product comprises a mixture of phosphate salts selected from the group consisting of calcium phosphate, potassium phosphate and sodium phosphate. More specifically, the calcium phosphate and potassium phosphates are dibasic, while the sodium phosphate may be a mixture of monobasic and dibasic. There is further disclosed a method for enhancing the fat loss in a mammal, said method comprising the administration of a composition comprising guggul extract, at least

one phosphate salt and at least one metabolic stimulant selected from the group consisting of Ma Huang, *Sida cordifolia*, coffee beans, green tea, guarave, cacao, bitter orange and mixtures thereof.

In a preferred embodiment, the weight control product according to the invention, comprises phosphatidylcholine, calcium phosphate (dibasic), potassium phosphate (dibasic), sodium phosphate (monobasic), sodium phosphate (dibasic), guggul extract, HCA, L-tyrosine, Ma Huang, green tea and bitter orange. In a preferred embodiment according to the invention, the guggul extract and the phosphate salts are in weight ratios of from 1:5 to 5:1 and the weight ratio of the guggul extract to the total amount of metabolic stimulant can range from 1:10 to 10:1.

Detailed Description of the Invention

As used herein "enteral administration" means consumption orally or application to the stomach or intestines. As used herein, "metabolic stimulant" means any compound that increases the metabolic rate of an animal. Representative compounds include ephedrine, pseudo-ephedrine, caffeine, synephrine, and herbal sources of said compounds such as Ma Huang, *Sida cordifolia*, coffee beans, green tea, guarave, cacao, bitter orange, Zhi Shi and the like.

As used herein "pharmaceutically acceptable" means that salts, drugs, medicaments, or other ingredients which the term describes are suitable for use in mammals without undue toxicity, incompatibility, instability, irritation, allergic

response, and the like, commensurate with a reasonable benefit/risk ratio.

As used herein and in the claims the term "therapeutically effective amount" means an amount of compound or composition sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. The therapeutically effectively amount of the compound or composition will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific compound or composition employed, the particular pharmaceutically acceptable compound utilized, and like factors within the knowledge and expertise of the medical community.

As used herein and in the claims the term "guggul extracts" means that composition extracted from the plants of the genus commiphora, particularly *Commiphora mukul* or *Commiphora wightii* or the chemically synthesized active components thereof. The guggul extract is obtained from the gum/resin of these plants, shrubs, or trees and is a complex mixture of terpenes, sterols, esters, and higher alcohols. The ethylacetate extract of the resin is an oily material also known as "gugulipid" or "guggul lipid". The pharmacological activity of gugulipid is attributed to two known ketonic steroids (the E- and Z-guggulsterones). The guggul extract contains from 5-50% by weight of the guggulsterones, more preferably at least 10% by weight. In an embodiment of the invention the "guggul extract" can be prepared in accordance with techniques known in the art. See, for example, EP0447,706.

As used herein and in the claims the term "vigor" means active bodily or mental strength or force. Vigor is also intensity of action and is evidenced by active, healthy, well balanced mental and physical states. Feelings of vigor or fatigue can be assessed through a Profile of Mood States questionnaire (POMS) (Educational and Industrial Testing Service, San Diego, CA). The POMS questionnaire has been validated as a method to determine significant differences in subjective feelings while patients undergo a clinical trial.

The weight control product according to the invention is enterally/orally administered to a mammal in need of weight control. The product according to the invention may also be consumed by individuals not in need of weight loss, but in need of reducing blood serum lipid and cholesterol levels. Further, individuals that would simply like to increase their energy levels or vigor, can benefit from the composition of this invention. The weight control product may be administered in the form a capsule, tablet, powder, liquid, food bar, soft gel capsule and the like. The form of administration is not important, however, dosages of at least 5 mg of guggul extract per kilogram of body weight and at least 15 mg of phosphate salt per kilogram of body weight should be administered daily. More preferably, the mammal is enterally administered at least 10 mg of guggul extract per kilogram of body weight and at least 20 mg of phosphate salts per kilogram of body weight per day. The amount of metabolic stimulant administered per day should be at least 10 mg, more preferably at least 50 mg and most preferably at least 100 mg per day. In one embodiment of the inventive dosage forms, e.g., capsules, could contain at least 10 mg of ephedrine and at least 100 mg of caffeine. The dosage form should be consumed at least twice,

more preferably at least 3 times per day. Thus, for a typical human of 70 kilograms the dose should be at least 350 mgs of guggul extract (assume 10% by weight guggulsterones) and at least 1050 mgs of phosphate salts per day and at least 50 mg of metabolic stimulant per day. A typical dose can range as high as 2 gms per day of the guggul extract, 3 gms per day for the phosphate salts and 1 gm per day of metabolic stimulant. In a preferred embodiment of the invention the daily dose of guggulsterones for an adult is about 75 mg, about 1,650 mg for the phosphate salts about 60 mgs of ephedrine, about 8 mg of synephrine and about 600 mgs of caffeine.

The phosphate salt component is preferably a mixture of sodium, potassium and calcium phosphates. The weight ratio of calcium phosphate to potassium phosphate to sodium phosphate can range from 5:1:5 to 1:5:1. A preferred weight ratio is about 2:1:1. The blend of the phosphate salts is designed to keep the mineral load from any one source, such as sodium, to a minimum and thus reduce the possibility of an electrolyte imbalance.

In a preferred embodiment, the weight ratio of ephedrine to caffeine can range from about 1:20 to about 1:5 and the weight ratio of ephedrine to synephrine can range from about 5:1 to about 1:1.

The L-tyrosine, useful in the weight control product of the present invention, is the naturally occurring laveorotatory amino acid. L-tyrosine is also known as

p-hydroxyphenylalanine of the molecular formula $C_9H_{11}NO_3$ and is a readily available amino acid that is typically obtained from protein hydrolysis. The amount of L-tyrosine consumed per day in the inventive formulation can range

from 5 to 100 mg per kilograms of body weight.

The phosphatidylcholine useful in the product according to the invention is also known as lecithin. Phosphatidylcholine is a polar lipid that occurs in crude fats and oils and is also associated with egg yolk. The phosphatidylcholine useful in the product of this invention can be derived from soybean oil and is readily available from commercial sources such as Lucas Meyer, Inc. of Decatur, Illinois. The phosphatidylcholine may be combined with other phospholipids such as phosphatidylserine, phosphatidylethanolamine and phosphatidylinositol can also be included in the inventive product. The dose of phosphatidylcholine per day is at least 0.1 mg, preferably at 1.0 mg per kg of body weight.

Garcinia cambosia is the preferred source of hydroxycitric acid. Hydroxycitric Acid (HCA) is a compound extracted from the rind of the fruit *Garcinia cambogia* or synthetically produced. Other sources of HCA include beet sugar, *Hibiscus sabdariffa*, *Garcinia indica* and *Garcinia atroviridus*. HCA is available commercially and can be prepared from the garcinia fruit peel in accordance with U.S. Patent 5,536,516. The ester and amide derivatives of HCA are also useful in the product according to the present invention. These derivatives are described in U.S. Patents 4,028,397 and 4,007,208.

The phosphates useful in the product according to the invention include the calcium, potassium and sodium phosphates. The monobasic and dibasic varieties are useful and the polyphosphates commonly have two or three phosphorus atoms per molecule but polymeric forms with more than twenty phosphorus atoms have application. As mentioned previously, the phosphate salts are preferably a mixture

of calcium, potassium and sodium salt.

The source of metabolic stimulant is preferably herbal, however, totally synthetic compounds are also useful. Most preferably, the ephedrine is supplied by the herbal extract known as Ma Huang and/or *Sida cordifolia* and the caffeine is supplied by green tea extract and/or guarave. Bitter orange and/or Zhi-Shi are also useful in the compositions according to the invention.

The present invention will be further illustrated by the following examples.

EXAMPLE I

Preparation of guggulsterone-phosphate salt product

The ingredients for making a 5.5 kg batch of the weight control product according to an embodiment of the invention is listed in Table 1. The extract of *Commiphora mukul* was obtained from Ayurveda of Bellevue, Washington. The extract was a cream colored powder and contained about 10.7% by weight gugulipids.

TABLE 1

Batch Preparation of Product

INGREDIENT	Gms
Lecithin (20% phosphatidylcholine)	437
Calcium Phosphate (dibasic 23%)	875
Potassium Phosphate (dibasic K^+ 44.8%, P 17.8%)	525
Sodium Phosphate (monobasic NA^{++} 9.16%)	262
Sodium Phosphate (dibasic Na^{++} 32%)	262
Guggul Extract (10% guggulsterones by wt.)	875
Garcinia Cambogia (50% hydroxycitric acid by wt.)	875
L-Tyrosine	875
Silicone Dioxide	35
Magnesium Stearate	70
Rice Powder	367

The first step in manufacturing this embodiment of the weight control product according to the invention was to mix all ingredients, except for the silicon dioxide and magnesium stearate, in a blender for 15 minutes. The silicon dioxide and the magnesium stearate were screened through a #40 mesh screen and then added to the blender. Blending continued for an additional 10 minutes and then the weight loss product was placed into #00 hard gelatin capsules for a gross weight of 860 mg per capsule. The dose per capsule of the various active components is found in Table 2.

TABLE 2

Gelatin Capsules

INGREDIENT	Dose per Capsule
Phosphatidylcholine	12.5 mg
Calcium Phosphate (dibasic 23%)	125.0 mg
Potassium Phosphate (dibasic K^+ 44.8%, P 17.8%)	75.0 mg
Sodium Phosphate (monobasic NA^{++} 9.16%)	37.5 mg
Sodium Phosphate (dibasic Na^{++} 32%)	37.5 mg
Guggul Extract (10% guggulsterones by wt.)	125.0 mg
Garcinia Cambogia (50% hydroxycitric acid by wt.)	125.0 mg
L-Tyrosine	125.0 mg

EXAMPLE 2

Clinical Study

This experiment was conducted to determine the effects of the guggul extract/phosphate salt weight loss product of the present invention on body composition, plasma lipid levels and mood states in overweight hyperlipidemic adults. A double blind, placebo controlled protocol was developed wherein twenty (20) subjects with a body mass index (BMI) of greater than twenty five (>25) were divided into three groups. Group A received 750 mgs of guggul extract and 1,650 mgs phosphate daily (6 capsules from Table 2). Group B received a maltodextrine placebo while Group C received nothing (control) for six weeks. The subjects were instructed by a registered dietitian to follow an American Heart Association Step One Diet and a three day per week circuit exercise program which was supervised by an exercise physiologist.

Subjects were excluded from the study if they were currently following a reduced calorie diet, were taking anorectic medications (i.e. phentermine,

silbutramine, etc.), had a history of thyroid disease, HIV/AIDS, cancer or any wasting syndrome. Subjects were also excluded if they had never exercised before. Capsules for Group A and Group B were the same in terms of size, shape, color and weight. Each group was instructed to take six capsules per day, two with each main meal.

Each subject was evaluated at baseline, week 3, week 6, and conclusion. Total body weight was measured using a Detecto™ balanced medical scale at each laboratory visit. Subjects were weighed after a four hour fast and voiding of the bladder. After four hours of fasting, body composition was measured via bioelectric impedance analysis (Biodynamics 3.10, Seattle, WA). All participants refrained from caffeine the day prior to body composition analysis and subjects were prohibited from drinking alcohol throughout the study.

All subjects engaged in a three day a week circuit training exercise program under the guidance of an exercise physiologist. The exercise sessions lasted for about forty-five (45) minutes. The exercise program consisted of a combination of step aerobics and weight training. The subjects were requested to stay on the 1800 calorie American Heart Association Step One Diet and were given meal plans, daily menus and restaurant guidelines. Each subject also was followed up with a telephone call from a registered dietitian and multiple twenty-four (24) hour dietary recalls were also taken at baseline, week three and week six.

Perceived Energy

The subjects of the study were also evaluated to determine if the inventive weight control product had any impact on the subjects' feelings of vigor or fatigue. A Profile of Mood States questionnaire (POMS) was employed to determine if the supplementation had any impact on these feelings. The questionnaire was from the Educational and Industrial Testing Service of San Diego, CA. The POMS questionnaire has previously been validated as a method to determine significant differences in subjective feelings while participating in a study. Each subject took the POMS at each laboratory visit.

Biochemical Parameters

Serum chemistries, complete blood count, total cholesterol and triglycerides were assessed at baseline, week 3, and week 6 during scheduled laboratory visits. The blood was drawn via the antecubital vein and processed by Quest Diagnostics, Wallingford, CT. Urinalysis was also conducted at each laboratory visit (Chemstrip Analyzer, Indianapolis, IN) and tested for any affect on urinary glucose or protein. Specific gravities were also measured as an indication of concentrated urine and dehydration.

Statistical analysis was conducted for each group and was tested for intergroup and intragroup variance. Fisher's Exact Test was utilized for baseline characteristics of the three groups while a Kruskal-Wallis Test was employed to test the continuous variables. Significance was set at a p value of <0.05. A total of twenty (20) patients enrolled however, two subjects dropped out, therefore, a total of eighteen (18) patients completed the study.

Results

The treatment group (Group A) lost a significant amount of body weight as compared to the placebo and controls groups. Group A lost 3.14% body weight ($p<0.05$). Group A lost a total of 2.54 kg (5.59 pounds) or 0.4 kg (0.9 pounds) per week. Group A also had a significant reduction in their fatigue as compared to other groups, that is, they felt less tired over time with the supplement according to the present invention. Group A also experienced a significant increase in vigor as they felt more energetic (24%) over time with the supplement. A significant decrease in body fat was also seen in Group A. All three groups lost a percentage of body fat however, Group A lost twice as much body fat than the placebo or control groups - A=3.8%; B=1.78%; C=1.75%; ($p<0.01$). In terms of actual fat weight loss, Group A lost 4.3 kg (9.48 pounds) of actual fat whereas the placebo group lost 1.36 kg (3 pounds) and the control group lost 1.22 kg (2.9 pounds) ($p<0.01$). The magnitude of lost fat for Group A was therefore three times that of all other groups. From another prospective, Group A lost 63% more fat than the placebo and control groups. An analysis of the blood chemistries also demonstrated that Group A experienced a trend towards better blood sugar values and that thyroid efficiency improved somewhat.

EXAMPLE 3

Comparative Analysis

This experiment is conducted to determine the active components of the composition disclosed in Table 2. In a manner similar to that described in Example 1, four formulas are prepared wherein Formula A is according to Table 1 in Example 1, Formula B omitted the calcium salts and the guggul extract, Formula C omitted the guggul extract and Formula D omitted the phosphate salts. The omitted substance is replaced with maltodextrin to keep the per capsule dosages for the remaining components identical. The clinical study is similar to that disclosed in Example 2, however, the study group is divided into 4 groups. Group A received six capsules daily of the formula disclosed in Table 1, while Groups B, C and D received six capsules of Formula B, C and D respectively. Table 3 sets forth the compositions of Formulae B, C and D.

TABLE 3

INGREDIENT	DOSE PER CAPSULE FORMULA B	DOSE PER CAPSULE FORMULA C	DOSE PER CAPSULE FORMULA D
Phosphatidylcholine	12.5 mg	12.5 mg	12.5 mg
Calcium Phosphate (dibasic 23%)	0	125.0 mg	0
Potassium Phosphate (dibasic K^+ 44.8%, P 17.8%)	0	75.0 mg	0
Sodium Phosphate (monobasic Na^{++} 9.16%)	0	37.5 mg	0
Sodium Phosphate (dibasic Na^{++} 32%)	0	37.5 mg	0
Guggul Extract (10% guggulsterones by wt.)	0	0	125.0 mg
Garcinia Cambogia (50% hydroxycitric acid by wt.)	125.0 mg	125.0 mg	125.0 mg
L-tyrosine	125.0 mg	125.0 mg	125.0 mg
Maltodextrin	400.0 mg	125.0 mg	275.0 mg

In terms of actual fat weight loss Group A will lose about 4.3 kg, Group B about 1.3 kg, Group C about 1.4 kg and Group D about 1.6 kg of fat. This test evidences that the combination of the guggul extract and the phosphate salts is critical to the extraordinarily high loss of body fat in the subjects. The guggul extract interacts synergistically with the phosphate salts to result in enhanced weight and fat loss. Similar to the results found in Example 2, the POMS ratings of Group A are significantly better than Groups B, C and D. In conclusion, the guggul extract/phosphate salt weight loss product improved mood states with

favorable body composition changes.

EXAMPLE 4

Preparation of Guggulsterone-Phosphate Salt –Metabolic Stimulant Product

Using the process described in Example 1, two (2) products were prepared, one with metabolic stimulants and one without. The products were placed in #00 clean/clear capsules and contained the components and amounts listed in Tables 4 and 5.

TABLE 4

Preparation of Product With a Metabolic Stimulant

INGREDIENT	Amount per Capsule
Phosphatidylcholine (35%)	71.4 mg
Dicalcium phosphate	135.72 mg
Dipotassium phosphate	67.5 mg
Sodium phosphate	33.75 mg
Disodium phosphate	33.75 mg
Gugulipid	125 mg
Garcinia Cambogia (50% HCA)	75 mg
L-tyrosine	125 mg
Sida cordifolia (6%)	50 mg
Green tea (50%)	50 mg
Citrus aranthium (8%)	1.5 mg
Citrin (magnesium potassium salt)	125 mg

Other Ingredients

Magnesium stearate
Microcrystalline cellulose
Rice flour
Gelatin

TABLE 5

Preparation of Product Without a Metabolic Stimulant

INGREDIENT	Amount per Capsule
Phosphatidylcholine (35%)	71.4 mg
Dicalcium phosphate	150.8 mg
Dipotassium phosphate	75 mg
Sodium phosphate	37.5 mg
Disodium phosphate	37.5 mg
Gugulipid	125 mg
Garcinia Cambogia (50% HCA)	125 mg
L-tyrosine	125 mg
Citrin (magnesium potassium salt)	125 mg

Other Ingredients

Magnesium stearate
Microcrystalline cellulose
Rice flour
Gelatin

EXAMPLE 5

Clinical Study

This experiment is conducted to determine the effects of the guggul extract/phosphate salt weight loss product as set forth in Table 5 against the guggul extract/phosphate salt/metabolic stimulant product as set forth in Table 4. A double blind, placebo controlled protocol is developed wherein twenty (20) subjects, with a body mass index (BMI) of greater than 25 are divided into three (3) groups. Group A receives 6 capsules from Table 4. Group B receives a maltodextrine placebo while Group C receives 6 capsules from Table 5 for six (6) weeks. The subjects are instructed by a registered dietitian to follow an American Heart Association Step One Diet and three day per week circuit exercise program which is supervised by an exercise physiologist.

Subjects are excluded from the study if they are currently following a reduced calorie diet, are taking anorectic medications (i.e., phentermine, silbutramine, etc.), have a history of thyroid disease, HIV/AIDS, cancer or any wasting syndrome. Subjects are also excluded if they had never exercised before. Capsules for each group are the same in terms of size, shape, color and weight. Each group is instructed to take six capsules per day. The general protocol set forth in Example 2 is followed in this Example.

Perceived Energy

The subjects of the study are also evaluated to determine if the weight control product, including the metabolic stimulants, have any impact on the subjects' feelings of vigor or fatigue. A Profile of Mood States questionnaire (POMS) is employed to determine if the supplementation has any impact on these feelings. The questionnaire is from the Educational and Industrial Testing Service of San Diego, California. The POMS questionnaire has previously been validated as a method to determine significant differences in subjective feelings while participating in a study. Each subject will take the POMS at each laboratory visit.

Biochemical Parameters

Serum chemistries, complete blood count, total cholesterol and triglycerides are assessed at baseline, week 3 and week 6 during scheduled laboratory visits as set forth in Example 2.

Statistical analysis will be conducted for each group and will be tested for intergroup and intragroup variance. Fisher's Exact Test will be utilized for baseline characteristics of the three groups while a Kruskal-Wallis Test will be employed to test the continuous variables. Significance will be set at a p value of <0.05.

Results

The treatment group (Group A) will lose a significant amount of body weight as compared to Group B, the placebo group. Group A will lose a total of about 2.8 kg, or almost 0.5 kg per week. Group C will also have a significant reduction in their weight as compared to Group B. Groups A and C will also feel less tired over time with the supplements according to the present invention. Group A will also experience a significant increase in vigor as they felt more energetic (about 30%) over time with the supplement of Table 4. A significant decrease in body fat will also be seen in Groups A and C. All three groups will lose a percentage of body fat, however, Group A will lose almost twice as much body fat as Group B (placebo).

Industrial Applicability

The synergistic weight control product of the invention which includes at least one metabolic stimulant, provides an unexpected benefit in weight loss and fat loss. The medical community and consumers at large will readily accept the inventive product as it provides outstanding results and is economically produced.

While certain representative embodiments and details have been described for the purpose of illustrating the invention, it will be apparent to those skilled in the art that various changes and modifications may be made therein without departing from the spirit or scope of the invention.

I claim:

1. A weight control product comprising guggul extract, at least one metabolic stimulant and at least one phosphate salt.

2. A composition comprising guggul extract, at least one metabolic stimulant and at least one phosphate salt selected from the group consisting of sodium phosphate, potassium phosphate and calcium phosphate.

3. The weight control product according to claim 1 additionally comprising at least one component selected from the group consisting of phosphatidylcholine, hydroxycitric acid and L-tyrosine.

4. The weight control product according to claim 1 wherein said metabolic stimulants are selected from ephedrine, pseudo-ephedrine, caffeine, synephrine and mixtures thereof and wherein said phosphate salts are selected from the group consisting of calcium phosphate, potassium phosphate and sodium phosphate.

5. The weight control product according to claim 1 wherein said metabolic stimulants are selected from Ma Huang, *Sida cordifolia*, coffee beans, green tea, guarave, cacao, bitter orange, Zhi Shi and mixtures thereof.

6. The method for enhancing the mood states and vigor of a mammal, said method comprising the enteral administration of a composition according to claim 2.

7. The method, according to claim 6, wherein said composition additionally comprises at least one component selected from the group consisting of phosphatidylcholine, hydroxycitric acid and L-tyrosine.

8. The method according to claim 6 wherein said phosphate salt is a mixture

of sodium phosphate, potassium phosphate, calcium phosphate and said metabolic stimulant is selected from ephedrine, pseudo-ephedrine, caffeine, synephrine and mixtures thereof.

9. The method according to claim 6 wherein said phosphate salts are a mixture of calcium phosphate dibasic, potassium phosphate dibasic, potassium phosphate dibasic, sodium phosphate monobasic and sodium phosphate dibasic; and wherein said metabolic stimulant is selected from Ma Huang, *Sida cordifolia*, coffee beans, green tea, guarave, cacao, bitter orange, Zhi Shi and mixtures thereof.

10. The method for enhancing fat loss in a mammal, said method comprising the administration of a composition according to claim 2.

11. The method according to claim 10 wherein said composition additionally comprises at least one component selected from the group consisting of phosphatidylcholine, hydroxycitric acid and L-tyrosine.

12. The method according to claim 10 wherein said phosphate salts are a mixture of sodium phosphate, potassium phosphate and calcium phosphate and wherein said metabolic stimulants are selected from ephedrine, pseudo-ephedrine, caffeine, synephrine and mixtures thereof.

13. A composition comprising guggul extract, at least two phosphate salts, at least one component selected from the group consisting of phosphatidylcholine, hydroxycitric acid and L-tyrosine and at least one metabolic stimulant selected from ephedrine, pseudo-ephedrine, caffeine, synephrine and mixtures thereof.

14. The product according to claim 1 wherein the weight ratios of said guggul extract to said phosphate salt is from 1:5 to 5:1.

15. The product according to claim 14 wherein said guggul extract contains from 5 to 50% by weight of guggulsterones.

16. The product according to claim 14 wherein said extract is an ethylacetate extract of resin from a plant selected from *Commiphora mukul* and *Commiphora wightii*.

17. The product according to claim 16 wherein said phosphate salt is a mixture of calcium phosphate, potassium phosphate and sodium phosphate at a weight ratio of from 5:1:5 to 1:5:1 and said metabolic stimulant is selected from Ma Huang, *Sida cordifolia*, coffee beans, green tea, guarave, cacao, bitter orange, Zhi Shi and mixtures thereof.

18. The product according to claim 17 additionally comprising at least one component selected from phosphatidylcholine, hydroxycitric acid and L-tyrosine.

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(54) Title: WEIGHT CONTROL PRODUCT COMPRISING A SYNERGISTIC MIXTURE OF GUGGUL EXTRACT, PHOSPHATE SALT AND METABOLIC STIMULANT

(57) Abstract: This invention relates to a weight control composition, preferably in the form of a capsule or tablet, comprising a mixture of guggul extract, at least one phosphate salt selected from calcium phosphate, potassium phosphate and sodium phosphate and at least one metabolic stimulant. The composition evidences synergistic activity in reducing body weight and percent body fat in mammals. The guggul extract/phosphate salt/metabolic stimulant product also reduces plasma lipid levels and cholesterol in overweight hyperlipidemic humans. The inventive composition may also contain at least one additional component selected from phosphatidylcholine, hydroxycitric acid and L-tyrosine.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 35/78, 31/56, 31/133, 31/135, 31/522, 31/685, 33/42.
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/602, 195.1, 196.1, 601, 603, 604, 605, 606; 514/78, 169, 170, 171, 177, 263, 264, 556, 561, 567, 574, 649, 909.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 447 706 A1 (CIPLA LIMITED) 25 September 1991, see page 2, lines 4-49.	1-18
Y	SATYAVATI, G.V. Guggulipid: a Promising Hypolipidaemic Agent from Gum Guggul (Commiphora wightii). Economic and Medicinal Plant Research. 1991, Vol. 5, pages 47-82, especially page 70.	1-18
Y	WEIL, A. A comprehensive Manual For Wellness and Self-Care. In: Natural Health, Natural Medicine. Houghton Mifflin Company (New York) 1995, pages 47, 62-64, entire document.	1-18
Y	NAZAR, K. et al. Phosphate supplementation prevents a decrease of triiodothyronine and increases resting metabolic rate during low energy diet. J. Physiol. Pharmacol. 1996, Vol. 47, No. 2, pages 373-383, entire document.	1-18

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KACIUBA-USCILKO et al. Effect of phosphate supplementation on metabolic and neuroendocrine responses to exercise and oral glucose load in obese women during weight reduction. Journal of Physiology and Pharmacology. 1993, Vol. 44, No. 4, pages 425-440, entire document.	1-18
Y	CA 2,038,929 A1 (TSUKAGOSHI et al.) 19 March 1992, see pages 1-4 and 8.	1-18
Y	US 5,422,352 A (ASTRUP) 06 June 1995, see columns 2-5.	1-18
Y	US 5,019,594 A (WURTMAN et al.) 28 May 1991, see columns 1-2.	1-18

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